[redacted]

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

Ravgen, Inc., *Plaintiff*, v. Natera, Inc. and NSTX, Inc., *Defendant*.	C.A. No. 1:20-cv-00692-ADA JURY TRIAL DEMANDED

NATERA'S AMENDED ANSWER, DEFENSES, AND COUNTERCLAIMS TO RAVGEN'S COMPLAINT FOR PATENT INFRINGEMENT

Defendants Natera, Inc. and NSTX, Inc. ("Natera" or "Defendants"), by and through their undersigned counsel, hereby respond to Plaintiff Ravgen Inc.'s ("Ravgen" or "Plaintiff") Complaint for Patent Infringement ("Complaint").

As an initial matter, Natera denies each and every allegation contained in the Complaint that is not expressly admitted below. Any factual allegation admitted below is admitted only as to the specific facts, and not as to any purported conclusions, characterizations, implications, or speculations that might follow from the admitted facts. Additionally, to the extent that the headings or any other non-numbered statements in the Complaint contain any allegations, Natera denies each and every such allegation. Natera includes headings herein solely for purposes of clarity. In addition, to the extent the allegations in the Complaint purport to characterize the nature and/or contents of the exhibits attached to the Complaint, the exhibits speak for themselves, and Natera is without sufficient knowledge to confirm, and therefore denies, whether those exhibits are indeed what they purport to be.

NATURE OF THE ACTION

1. Natera admits that the Complaint purports to state a claim for patent infringement of U.S. Patent Nos. 7,727,720 (the "'720 Patent") and 7,332,277 (the "'277 Patent") arising under

the Patent Laws of the United States, 35 U.S.C. §§ 271, *et seq.* Natera denies any remaining allegations of paragraph 1.

THE PARTIES

2. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 2, and therefore denies them.

3. Natera admits that Natera, Inc. is a corporation organized under the laws of Delaware and that Natera, Inc. has a place of business at 201 Industrial Road, Suite 410, San Carlos, California 94070. Natera admits that Natera, Inc. is registered to do business in the state of Texas. Natera further admits that Natera, Inc. has appointed National Registered Agents, Inc., 1999 Bryan St., Ste. 900 Dallas, TX 75201 as its agent for service of process. Natera admits that exhibit 11 appears to be a printout from https://www.builtinaustin.com/company/natera, stating, *inter alia*, "13011A McCallen Pass, Austin, TX 78753." Natera also admits that exhibit 12 appears to be a printout from https://www.natera.com/hrzn27c, stating, *inter alia*, "CLIA ID number 45D2093704." Natera is unsure what Ravgen means by "maintains" and therefore denies any remaining allegations of paragraph 3.

4. Natera admits that NSTX, Inc. is a corporation organized under the laws of Delaware and that NSTX, Inc. has a place of business at 13011 McCallen Pass, Building A, Austin, TX 78753. Natera admits that NSTX, Inc. is registered to do business in the state of Texas. Natera further admits that NSTX, Inc. has appointed National Registered Agents, Inc., 1999 Bryan St., Ste. 900 Dallas, TX 75201 as its agent for service of process. Natera also admits that NSTX, Inc. is a wholly-owned subsidiary of Natera, Inc. Natera denies any remaining allegations of paragraph 4.

5. Natera admits that it offers products under the tradenames Panorama, Vistara, Signatera, and Prospera. Natera admits that it offers those products in the United States, and that

Natera includes certain statements relating to those products on its website, www.natera.com. Natera admits that exhibit 14, which appears to be a printout from https://www.natera.com/womens-health/panorama-nipt-prenatal-screening, states, *inter alia*, "Panorama is a blood-based genetic test of the pregnant mom that screens for common chromosomal conditions that affect a baby's health." Natera also admits that exhibit 15, which appears to be a printout from https://www.natera.com/womens-health/vistara-nipt-single-gene-test, states, *inter alia*, that the product marketed under the tradename Vistara "identifies risk for single gene disorders." Natera further admits that exhibit 16, which appears to be a printout from https://www.natera.com/oncology/signatera-advanced-cancer-detection, states, *inter alia*, that the product marketed under the tradename Signatera is "optimized to detect circulating tumor DNA (ctDNA) for molecular residual disease (MRD) assessment and recurrence monitoring for patients previously diagnosed with cancer." Natera admits that exhibit 17, which appears to be a printout from https://www.natera.com/organ-transplantation/prospera-organ-transplantation-assessment, *inter alia*, refers to the product marketed under the tradename "Prospera," and states "Prospera is thoughtfully optimized to be a precise and reliable tool for early, clinically meaningful rejection assessment." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 5, and therefore denies them.

JURISDICTION AND VENUE

6. Natera admits that Ravgen has re-alleged the allegations stated in paragraphs 1-5 of its Complaint. Natera hereby incorporates its responses to paragraphs 1-5 of the Complaint.

7. Natera admits that the Complaint purports to state a claim for patent infringement arising under the Patent Laws of the United States, including 35 U.S.C. §§ 271, *et seq.* Natera further admits that this Court has subject matter jurisdiction over causes of action for alleged patent infringement pursuant to 28 U.S.C. §§ 1331 and 1338(a). Natera denies any remaining allegations

of paragraph 7, and specifically denies that it has committed any acts of infringement in this District.

8. Natera does not contest that venue is proper in this District pursuant to U.S.C. §§ 1391(b), (c), (d), and 1400(b) for purposes of this action only. Natera denies any remaining allegations of paragraph 8, and specifically denies that it has committed any acts of infringement in this District.

9. Natera admits that Natera Inc. and NSTX Inc. are registered to conduct business in Texas and that NSTX, Inc. has a place of business in Austin, Texas. The remaining averments of paragraph 9 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies these averments.

10. Natera admits that exhibit 11 appears to be a printout from https://www.builtinaustin.com/company/natera, stating, *inter alia*, "13011A McCallen Pass, Austin, TX 78753." Natera also admits that exhibit 12 appears to be a printout from https://www.natera.com/hrzn27c, stating, *inter alia*, "CLIA ID number 45D2093704." Natera is unsure what Ravgen means by "maintains" and therefore denies the remaining allegations of paragraph 10.

11. Natera admits that NSTX, Inc. has a place of business at 13011 McCallen Pass, Building A, Suite 110, Austin, TX 78753. Natera further admits that said place of business is CLIA certified and its CLIA number is 45D2093704. Natera admits that exhibit 18, which appears to be a printout from http://investor.natera.com/static-files/97e03872-d617-4ba8-b7ea-18a52f368eae, states, *inter alia*, "In September 2015, the Company's subsidiary entered into a long-term lease agreement for laboratory and office space totaling approximately 94,000 square feet in Austin, Texas." Natera admits that paragraph 11 contains what appears to be excerpts from

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_ Laboratory_ Demographic _Information and https://www.cdc.gov/clia/LabSearch.html. Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 11, and therefore denies them.

12. Natera admits that paragraph 12 contains what appears to be two images of a building with a sign listing the address "13011 McCallen Pass, Building A." Natera admits that the sign in the first image in paragraph 12 lists, *inter alia*, "natera" and "NSTX," and the building also bears a sign of the word "natera." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 12, and therefore denies them.

13. Natera admits that exhibit 21, which appears to be an undated printout from https://www.natera.com/careers/job-openings, lists, *inter alia*, job openings at Natera, Inc. in Austin, TX, including "Medical Laboratory Scientist I" under the heading "NIPT Panorama (NIPT)," "Associate Laboratory Director" under the heading "LBAF," "Technical Product Manager R&D – Oncology LIMS" under heading "Engineering (ENGR)," and "Laboratory Operations Manager" under heading "Molecular Bio Labs Ops (MBLO)." Natera further admits that exhibit 22, which appears to be a printout of https://www.natera.com/careers/job-openings?gnk=job&gni=8a78879e67ebaa7a016811bdc9a84f86&lang=en, states, *inter alia*, that the "Associate Laboratory Director" position's "Primary Responsibilities" include "[r]eview, approve, and sign-out reports for a variety of clinical molecular/cytogenetic and/or oncologic results, including NIPT, carrier screening, PGD/PGS, products of conception and oncology testing on platforms including SNP array analysis, NGS, and other methodologies" and "[p]rovide clinical and technical support for genetic counselors and other laboratory personnel." Natera admits that

exhibit 23, which appears to be a printout of https://www.natera.com/careers/job-openings?gnk=job&gni=8a78839f7184b92601718aa644fb6b8c&lang=en, stating, *inter alia*, "Technical Product Manager R&D – Oncology LIMS" and "[f]or this position focused on Oncology LIMS, you will be working on projects and maintenance for LIMS related to our Signatera cancer detection product." Natera further admits that exhibit 24, which appears to be a printout of https:www.linkedin.com/jobs/view/prospera-clinical-operations-coordinator-at-natera-1450349453/, states, *inter alia*, "Prospera Clinical Operations Coordinator," "Austin, TX," and "[n]o longer accepting applications." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 13, and therefore denies them.

14. Natera admits that it offers products under the tradenames Panorama, Vistara, Signatera, and Prospera in the United States, and that it lists those products on its website, www.natera.com. Natera is without knowledge to confirm whether that website is accessible in this District, and therefore denies that allegation. Natera denies the remaining allegations of paragraph 14, and specifically denies that these products employ methods claimed in the Patents-in-Suit.

15. Natera denies that Natera, Inc. and NSTX, Inc. have committed acts of direct infringement in this judicial District. Natera further denies that Natera, Inc. and NSTX, Inc. perform infringing methods in this District by using the Panorama products, including processing the results of those products at 13011 McCallen Pass, Building A, Austin, TX 78753. Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 15, and therefore denies them. The remaining averments of paragraph 15

constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

16. Natera denies that NSTX, Inc. has committed acts of direct infringement in this Judicial District. Natera further denies that NSTX, Inc. performs infringing methods in this District by using the Panorama products, including processing the results of those products at 13011 McCallen Pass, Building A, Austin TX 78753. Natera denies any remaining allegations of paragraph 16.

17. Natera admits that NSTX, Inc. is a wholly-owned subsidiary of Natera, Inc. Natera denies that Natera Inc. and NSTX, Inc. have participated in the commission of patent infringement in this judicial District, including by making, using, offering for sale, and/or selling the Panorama, Vistara, Signatera, and Prospera tests in this District and elsewhere that led to foreseeable harm and injury to Ravgen. Natera admits that Matthew Rabinowitz is the current Executive Chairman of the board of directors of Natera, Inc. Natera further admits that exhibit 13, which appears to be a Form 10-Q filed on behalf of Natera, Inc. for the quarterly period ending on September 30, 2017, purports to show Matthew Rabinowitz as a signatory to a "Pledge and Security Agreement" dated August 8, 2017, as "Chief Executive Officer" of Natera, Inc. and NSTX, Inc. Natera admits that Michael Brophy is currently the Chief Financial Officer at Natera, Inc. Natera also admits that exhibit 25, which appears to be a Form 10-Q filed on behalf of Natera, Inc. for the quarterly period ending September 30, 2019, purports to show Michael Brophy as a signatory to a "Third Amendment" dated September 12, 2019, as "Chief Financial Officer" of Natera, Inc. and NSTX, Inc. Natera admits that Jonathan Sheena is currently the Chief Technology Officer at Natera, Inc. Natera admits that exhibits 9 and 10 identify Jonathan Sheena as "CTO." Natera also admits that exhibits 9 and 10, which are undated, identify Jonathan Sheena, Roelof Botha, Todd Cozzens,

Edward C. Driscoll, James I. Healy, John Steuart, Gail Marcus and Herm Rosenman each as "Director." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 17, and therefore denies them. The remaining averments of paragraph 17 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

18. Natera does not contest that Natera, Inc. is subject to this Court's jurisdiction for this action only. Natera denies that Natera, Inc. conducts business in this District by at least offering for sale and selling products and services that practice the claimed inventions of the Patents-in-Suit, including the Panorama, Vistara, Signatera, and Prospera products. Natera further denies that Natera, Inc. leases and operates offices and laboratories in this District that support and process products and services that practice the claimed inventions of the Patents-in-Suit, including at least the Panorama product. The remaining averments of paragraph 18 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

19. Natera does not contest that this Court has personal jurisdiction over Natera, Inc. for this action only. The remaining averments of paragraph 19 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

20. Natera does not contest that this Court has personal jurisdiction over Natera, Inc. for this action only. Natera denies the remaining allegations of paragraph 20.

21. Natera does not contest that NSTX, Inc. is subject to this Court's jurisdiction for this action only. Natera denies that NSTX, Inc. conducts business in this District by at least offering for sale and selling products and services that practice the claimed inventions of the Patents-in-Suit, including the Panorama test. Natera further denies that NSTX, Inc. leases and

operates offices and laboratories in this District that support and process products and services that practice the claimed inventions of the Patents-in-Suit, including the Panorama test. The remaining averments of paragraph 21 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

22. Natera does not contest that this Court has personal jurisdiction over NSTX, Inc. for this action only. The remaining averments of paragraph 22 constitute conclusions of law to which no response is required. To the extent a response is required, Natera denies those averments.

23. Natera does not contest that this Court has personal jurisdiction over NSTX, Inc. for this action only. Natera denies the remaining allegations of paragraph 23.

BACKGROUND OF THE INVENTION

24. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 24, and therefore denies them.

25. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 25, and therefore denies them.

26. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 26, and therefore denies them.

27. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 27, and therefore denies them.

28. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 28, and therefore denies them.

29. Natera admits that exhibit 27 to the Complaint, which appears to be an article, states, *inter alia*, "[t]he methods described herein for increasing the percentage of free fetal DNA provide a solid foundation for the development of a noninvasive prenatal diagnostic test." Natera denies that exhibit 27 states, *inter alia*, "[t]he method described herein for increasing the

percentage of cell-free fetal DNA provide a solid foundation for the development of a noninvasive prenatal diagnostic test." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 29, and therefore denies them.

30. Natera admits that paragraph 30 includes a reproduction of two separate excerpts from exhibit 28 to the Complaint. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 30, and therefore denies them.

31. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 31, and therefore denies them.

32. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 32, and therefore denies them.

33. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 33, and therefore denies them.

PATENTS-IN SUIT

34. Natera admits that Ravgen has re-alleged the allegations stated in paragraphs 1-33 of its Complaint. Natera hereby incorporates its responses to paragraphs 1-33 of the Complaint.

35. Natera admits that exhibit 1 to the Complaint appears to be a copy of the '277 Patent. Natera further admits that on its face, the '277 Patent is entitled "Methods for Detection of Genetic Disorders." Natera admits that on its face, the '277 Patent: states that it was issued on February 19, 2008, states that the inventor of the '277 Patent is Ravinder S. Dhallan, and states that the '277 Patent is assigned to Ravgen, Inc. Natera denies the remaining allegations of paragraph 35.

36. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 36, and therefore denies them.

37. Natera admits that exhibit 2 to the Complaint appears to be a copy of the '720 Patent. Natera further admits that on its face, the '720 Patent: states that it was issued on June 1, 2010, states that the inventor of the '720 Patent is Ravinder S. Dhallan, and states that the '720 Patent is assigned to Ravgen, Inc. Natera denies the remaining allegations of paragraph 37.

38. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 38, and therefore denies them.

39. Natera admits that paragraph 39 of the Complaint contains a reproduction of claim 81 of the '277 Patent. Natera denies the remaining allegations of paragraph 39.

40. Natera admits that paragraph 40 of the Complaint contains a reproduction of claim 1 of the '720 Patent. Natera denies the remaining allegations of paragraph 40.

41. Natera admits that paragraph 41 of the Complaint contains a reproduction of an excerpt from the '277 and '720 Patents at 32:24-39 and 33:31-46 respectively. Natera denies the remaining allegations of paragraph 41.

42. Natera admits that paragraph 42 of the Complaint contains a reproduction of an excerpt from the '277 and '720 Patents at 91:44-60 and 92:10-26 respectively, but that the reproduction omits the sentence "Two or more than two cell lysis inhibitors can be used," as found at 91:49-50 and 92:15-16 in the '277 and '720 Patents respectively. Natera denies the remaining allegations of paragraph 42.

43. Natera admits that paragraph 43 of the Complaint contains a reproduction of two excerpts from exhibit 5 to the Complaint, which appears to be an excerpt from the file history of the '720 Patent. Natera denies the remaining allegations of paragraph 43.

44. Natera denies the allegations of paragraph 44.

DEFENDANTS' ALLEGED INFRINGING ACTIVITIES

45. Natera admits that Ravgen has re-alleged the allegations stated in paragraphs 1-44 of its Complaint. Natera hereby incorporates its responses to paragraphs 1-44 of the Complaint.

A. The Accused Panorama Test

46. Natera admits that the product marketed under the tradename Panorama is a prenatal test that screens for common chromosomal conditions that may affect a baby's health. Natera admits that exhibit 34, which appears to be a print out of http://investor.natera.com/static-files/e8a10798-0960-45b6-909a-bc96cf9ea9f7 dated February 20, 2013, states, *inter alia*, "Natera, a leading innovator in reproductive and prenatal genetic testing, today announced that the company's non-invasive prenatal screening test, Panorama™, will launch on March 1 for the detection of trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome) and select sex chromosome abnormalities, such as monosomy X (Turner's syndrome)." Natera denies any remaining allegations of paragraph 46.

47. Natera admits that exhibit 34, which appears to be a print out of http://investor.natera.com/static-files/e8a10798-0960-45b6-909a-bc96cf9ea9f7 dated February 20, 2013, states, *inter alia*, "[t]he test uses fetal cell-free DNA found in maternal blood and works as early as nine weeks gestation." Natera denies any remaining allegations of paragraph 47.

48. Natera admits that exhibit 36, which appears to be a printout of https://www.natera.com/products/panorama-test?page=4, states, *inter alia*, "Panorama requires two cell-free DNA Streck tubes each filled with at least 10mL of the mother's blood." Natera admits that paragraph 48 includes a reproduction of an excerpt from exhibit 37, which appears to be a printout of https://www.natera.com/file/7891/download?token=udKvGaKP. Natera further admits that exhibit 38, which appears to be a printout of a Form 10-K Filing for the fiscal year ending December 31, 2019, states, *inter alia*, "Streck is the sole supplier of the blood collection

tubes included in our Panorama test under a supply arrangement with Streck under which we are required to exclusively use Streck tubes." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 48, and therefore denies them.

49. Natera admits that exhibit 39, which appears to be a printout from https://www.streck.com/products/stabilization/cell-free-dna-bct/#resources, states, *inter alia*, "Cell-Free DNA BCT is a direct draw blood collection tube which stabilizes nucleated blood cells. The unique preservative limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA. Cell-Free DNA BCT has also been demonstrated to minimize the degradation of circulating tumor cells (CTCs). By limiting cell lysis, the specialized chemistry provides sample integrity during storage, shipping and handling of blood samples. Cell-free DNA and gDNA are stable for up to 14 days at 6 °C to 37 °C. CTCs are stable for up to 7 days at 15 °C to 30 °C." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 49, and therefore denies them.

50. Natera admits that paragraph 50 includes reproductions of images from exhibits 35 and 40. Natera further admits that exhibit 41, which appears to be a printout of https://www.natera.com/press-releases/panorama-nipt-achieves-2-million-test-milestone, states *inter alia*, "Panorama reveals a baby's risk for severe genetic disorders as early as nine weeks into pregnancy. The test uses a unique single-nucleotide polymorphism (SNP)-based technology to analyze fetal/placental DNA obtained through a blood draw from the mother. It is the only test that differentiates between maternal and fetal DNA in the relevant chromosomes of interest." Natera admits that exhibit 43, which appears to be a printout of a publication published on May 7, 2014, states, *inter alia*, "Cell-free DNA was isolated from maternal plasma, amplified in a single

multiplex polymerase chain reaction assay that interrogated 19,488 SNPs covering chromosomes 13, 18, 21, X, and Y, and sequenced." Natera admits that exhibit 38, which appears to be a Form-10K filing for the fiscal year ending December 31, 2019, states, *inter alia*, "We extract DNA from each sample, amplify the specific SNPs that we are interested in measuring, and then sequence the DNA using NGS. Using our proprietary bioinformatics technology, we analyze the DNA sequences to assess the state of the fetal genome, focusing on the SNP data, while incorporating public information from the Human Genome Project. Our bioinformatics algorithm builds billions of detailed models of the potential genetic state of the sample to determine the most likely diagnosis. After Panorama generates its result, we provide the doctor or the laboratory with a simple report showing the risk that abnormalities are present in the fetus." Natera denies that exhibit 42, or the hyperlink provided for exhibit 42, displays a video. Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 50, and therefore denies them.

B. The Accused Vistara Test

51. Natera admits that exhibit 45, which appears to be a printout of https://natera.gcs-web.com/news-releases/news-release-details/natera-inc-announces-launch-vistara-single-gene-mutation-nipt dated May 8, 2017, states, *inter alia*, "Natera, Inc. Announces Launch of Vistara Single-Gene Mutation NIPT," and "Natera (NASDAQ: NTRA), a leader in genetic testing, announced the launch of Vistara, a non-invasive prenatal test (NIPT) to screen single-gene disorders. Vistara is a complement to Natera's market-leading Panorama® non-invasive prenatal test (NIPT) and screens for new mutations in 30 genes that have a combined incidence rate of nearly 1 in 600, which is higher than that of Down Syndrome." Natera further admits that exhibit 25, which appears to be a printout of a Form 10-Q for the quarterly period ending September 30,

2019, states, *inter alia*, "We began offering our Vistara single-gene mutations screening test in May 2017." Natera denies any remaining allegations of paragraph 51.

52. Natera admits that exhibit 46, which appears to be a printout of https://zotzklimas.de/images/vistara/VISTARA_Whie_Paper_englisch.pdf, states *inter alia*, "circulating cell-free fetal DNA in maternal blood." Natera further admits that exhibit 47, which appears to be a printout of http://www.elitekliinik.ee/eng/wp-content/uploads/sites/3/2018/10/POSITIVE-Vistara-Sample-Report.pdf, states, *inter alia*, "evaluates genetic information in the maternal blood, which is a mixture of maternal and placental DNA." Natera denies any remaining allegations of paragraph 52.

53. Natera admits that paragraph 53 includes a reproduction of an image from exhibit 48. Natera admits that exhibit 48 states, *inter alia*, "Maternal Sample" and "Two 10mL Tiger-top Streck Cell-Free DNA BCT® blood tubes." Natera denies any remaining allegations of paragraph 53.

54. Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 54, and therefore denies them.

55. Natera admits that exhibit 46 states, *inter alia*, "This tests screens for specific clinically significant and life-altering single gene disorders that are outside the scope of current non-invasive prenatal tests. A SNP-based fetal fraction calculation method was developed that yielded concordance with the established Y-chromosome method. We also demonstrate that this test can detect DNA changes in cell-free plasma DNA using a combination of spike-in samples and samples from pregnant women." Natera further admits that exhibit 46 states, "Once plasma cell-free DNA is extracted from maternal blood, molecular barcodes are used to add unique labels to the cell-free DNA molecules before PCR"; "For this assay, fetal fraction is calculated based on

the detection of the unique SNPs analyzed across the genome"; "This assay can accurately sequence cell-free DNA from the mother's plasma and can detect DNA changes (both benign and disease-causing) with a sensitivity and specificity >99%." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 55, and therefore denies them.

56. Natera admits that exhibit 38, which appears to be a Form 10-K for the fiscal year ending December 31, 2019, states, *inter alia*, "For example, a portion of our Horizon carrier screening testing and our Vistara single-gene mutations testing is performed by third-party laboratories. These third-party laboratories are subject to contractual obligations to perform these services for us, but are not otherwise under out control." Natera further admits that exhibit 46, states, *inter alia*, "Following development and validation, Natera collaborated with Baylor Genetics to assist in clinical introduction of the test, particularly in providing samples to help establish the lower limit of fetal fraction. This test is performed and reported by Baylor Genetics." Natera denies any remaining allegations of paragraph 56.

C. The Accused Signatera Test

57. Natera admits that exhibit 49, which appears to be a printout of https://www.natera.com/press-releases/natera-launches-signatera%E2%84%A2-personalized-circulating-tumor-dna-technology-cancer dated August 21, 2017, states, *inter alia*, "Natera launches Signatera Personalized Circulating Tumor DNA Technology for Cancer Research"; "Natera, Inc. (NASDAQ: NTRA), a leader in non-invasive genetic testing, today announced the launch of Signatera™, a circulating tumor DNA (ctDNA) technology that analyzes and tracks mutations specific to an individual's tumor, for research use only (RUO) by oncology researchers and biopharmaceutical companies. Already in clinical validation with multiple world-leading

cancer institutes, Signatera™ offers a novel personalized approach to cancer detection in plasma." Natera denies any remaining allegations of paragraph 57.

58. Natera denies the allegations of paragraph 58.

59. Natera admits that exhibit 50, which appears to be a printout of https://www.natera.com/oncology/signatera-research-pipeline, states, *inter alia*, "Two tubes of whole blood collected in Streck tubes or 10 mL of double-spun plasma." Natera admits that exhibit 51, which appears to be a printout of https://www.natera.com/sites/default/files/SGN_PositiveReport_Mockup.pdf, states, *inter alia*, "Circulating tumor DNA is extracted from plasma collected in Streck tubes using Natera's proprietary methods." Natera denies that exhibit 36 states, "We also only use Streck tubes for the primary analysis of Signatera results." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 59, and therefore denies them.

60. Natera is without knowledge or information sufficient to form a belief regarding the truth of the allegations of paragraph 60, and therefore denies them.

61. Natera admits that paragraph 61 of the Complaint includes a reproduction of an image from exhibit 52. Natera admits that exhibit 52 of the Complaint, which appears to be a printout of https://doi.org/10.1031/nature22364, states, *inter alia*, "Overview of the study methodology. Multi-region sequencing of NSCLC was performed as part of the TRACERx study. PCR assay panels were designed on the basis of the phylogenetic analysis, targeting clonal and subclonal SNVs to facilitate non-invasive tracking of the patient-specific tumor phylogeny. Assay panels were combined into multiplex assay pools containing primers from up to 10 patients. Cell-free DNA (cfDNA) was extracted from pre- and postoperative plasma samples and multiplex-PCR was performed, followed by sequencing of the amplicons. Findings were integrated with M-seq

exome data to track tumour evolution." Natera further admits that exhibit 50 states, *inter alia*, "Signatera residual disease test. The DNA sequence from your tumor tissue is compared to normal cells from your blood to determine the unique set of mutations specific to your tumor tissue." Natera admits that exhibit 51 states, *inter alia*, "Whole-exome sequencing using KAPA Hyper Prep library kit (Roche) with a custom xGen exome capture (IDT) is performed to identify tumor DNA sequence using a proprietary algorithm. Sixteen putative clonal variants present in the tumor but absent in the baseline DNA form the basis for individual-specific PCR-based assays. Individual-specific PCR assays are run to detect presence or absence of circulating tumor DNA (ctDNA). A patient's plasma sample is considered ctDNA positive when at least two individual-specific tumor variants are detected." Natera denies any remaining allegations of paragraph 61.

D. The Accused Prospera Test

62. Natera admits that exhibit 38 states, *inter alia*, "We received a final Medicare local coverage determination, or LCD, for Prospera in December 2019, covering all kidney transplant recipients, including those with multiple kidney transplants, and are working towards a full-scale commercial launch in 2020." Natera further admits that exhibit 58, which appears to be a printout ofhttps://www.natera.com/press-releases/natera-receives-final-medicare-coverage-prospera%E2%84%A2-organ-transplant-rejection dated December 19, 2019, states, *inter alia*, "Natera Receives Final Medicare Coverage for Prospera™ Organ Transplant Rejection Assessment Test" and "The Prospera test assesses the risk of active renal allograft rejection with greater precision than other biomarkers or other dd-cfDNA test on the market." Natera denies any remaining allegations of paragraph 62.

63. Natera admits that exhibit 17, which appears to be a printout of https://www.natera.com/organ/transplantation/prospera-organ-transplantation-assessment, states,

inter alia, "Prospera is powered by highly optimized, proprietary cell-free DNA (cfDNA) technology. As party of your toolkit to watch for signs of active rejection, Prospera assesses all types of kidney transplant rejection with great precision. . . . Simpler and less invasive than biopsy: Prospera measures the amount of donor DNA from a transplant recipient through a blood test." Natera denies any remaining allegations of paragraph 63.

64. Natera admits that exhibit 54, which appears to be a printout of https://www.natera.com/organ-transplantation/prospera-faq, states, *inter alia*, "Prospera requires two cell-free DNA Streck tubes each filled with at least 10mL of the patient's blood to achieve optimal performance." Natera further admits that paragraph 64 includes a reproduction of an image from exhibit 55. Natera further admits that exhibit 38 states, *inter alia*, "We also only use Streck tubes for the primary analysis of Signatera results, and for our Prospera test." Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 64, and therefore denies them.

65. Natera is without knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of paragraph 65, and therefore denies them.

66. Natera admits that paragraph 66 includes a reproduction of an image from exhibits 17 and 53. Natera further admits that exhibit 52 states, *inter alia*, "Prospera is powered by highly optimized, proprietary cell-free DNA (cfDNA) technology. As part of your tool kit, Prospera assesses all types of kidney transplant rejection with the greatest precision"; "Simpler and less invasive than biopsy." Natera denies that exhibit 52 states, "Prospera measures the amount of donor DNA from a transplant recipient through a blood test." Natera admits that exhibit 38 states, *inter alia*, "Our assay, Prospera, is designed to assess active rejection in patients who have undergone kidney transplantation by measuring the fraction of dd-cfDNA in the recipient's blood,

which can spike relative to background cfDNA when the transplanted organ is injured due to immune rejection." Natera further admits that exhibit 56, which appears to be a printout of https://doi.org/10.3390/jcm8010019, states, *inter alia*, "dd-cfDNA Measurement in Blood Samples. Cell-free DNA was extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen) and quantified on the LabChip NGS 5k kit (Perkin Elmer, Waltham, MA, USA) following manufacturer's instructions. Cell-free DNA was input into library preparation using the Natera Library Prep kit as previously described, with a modification of 18 cycles of library amplification to plateau the libraries. Purified libraries were quantified using LabChip NGS 5k as previously described. Target enrichment was accomplished using massively multiplexed-PCR (mmPCR) using a modified version of a previously described method, with 13,392 single nucleotide polymorphisms (SNPs) targeted. Amplicons were then sequenced on an Illumina HiSeq 2500 Rapid Run, 50 cycles single end, with 10-11 million reads per sample" and "In conclusion, this study validates the use of dd-cfDNA in the blood as an accurate marker of kidney injury/rejection across a range of pathologies with acute and chronic findings." Natera denies any remaining allegations of paragraph 66.

E. Defendants' Alleged Knowledge of the Ravgen Patents

67. Natera denies the allegations of paragraph 67.

68. Natera is currently investigating the truth of the allegations of paragraph 68 to the Complaint and is presently without information sufficient to admit or deny such allegations and on that basis denies them.

69. Natera denies that it has infringed the Patents-in-Suit and that it was aware of, or willfully blind to, the Patents-in-Suit or any such infringement as alleged. Natera is currently investigating the truth of the remaining allegations of paragraph 69 to the Complaint and is

presently without information sufficient to admit or deny such allegations and on that basis denies them.

70. Natera is currently investigating the truth of the allegations of paragraph 70 to the Complaint and is presently without information sufficient to admit or deny such allegations and on that basis denies them.

71. Natera is unsure what Ravgen means by "commercializing," and therefore denies the allegations relating thereto. Natera denies the remaining allegations of paragraph 71.

COUNT I
(ALLEGED INFRINGEMENT OF THE '277 PATENT)

72. Natera admits that Ravgen has re-alleged the allegations stated in paragraphs 1-71 of its Complaint. Natera hereby incorporates its responses to paragraphs 1-71 of the Complaint.

73. Natera denies the allegations of paragraph 73.

74. Natera denies the allegations of paragraph 74.

75. Natera denies the allegations of paragraph 75.

76. Natera denies the allegations of paragraph 76.

77. Natera denies the allegations of paragraph 77.

78. Natera denies the allegations of paragraph 78.

79. Natera denies the allegations of paragraph 79.

80. Natera denies the allegations of paragraph 80.

81. Natera denies the allegations of paragraph 81.

82. Natera denies the allegations of paragraph 82.

83. Natera denies the allegations of paragraph 83.

84. Natera denies the allegations of paragraph 84.

COUNT II
(ALLEGED INFRINGEMENT OF THE '720 PATENT)

85. Natera admits that Ravgen has re-alleged the allegations stated in paragraphs 1-84 of its Complaint. Natera hereby incorporates its responses to paragraphs 1-84 of the Complaint.

86. Natera denies the allegations of paragraph 86.

87. Natera denies the allegations of paragraph 87.

88. Natera denies the allegations of paragraph 88.

89. Natera denies the allegations of paragraph 89.

90. Natera denies the allegations of paragraph 90.

91. Natera denies the allegations of paragraph 91.

92. Natera denies the allegations of paragraph 92.

93. Natera denies the allegations of paragraph 93.

94. Natera denies the allegations of paragraph 94.

95. Natera denies the allegations of paragraph 95.

96. Natera denies the allegations of paragraph 96.

97. Natera denies the allegations of paragraph 97.

98. Natera denies the allegations of paragraph 98.

99. Natera denies the allegations of paragraph 99.

PRAYER FOR RELIEF

100. Natera denies that Ravgen is entitled to any of the relief sought in its prayer for relief against Natera. Ravgen's prayer should be denied in its entirety and with prejudice.

DEMAND FOR JURY TRIAL

101. Natera does not object to a trial by jury on all issues so triable.

102. All allegations not specifically admitted are denied.

AFFIRMATIVE DEFENSES

103. By asserting the following Defenses, the burden of proof has not shifted from Ravgen for any issue where Ravgen bears the burden, including, without limitation, infringement. Natera reserves the right to amend its response, including asserting additional affirmative and other defenses as they may be discovered or otherwise become available.

104. Non-Infringement. Natera has not infringed, either directly, indirectly, by inducing infringement of others, by contributing to the infringement of others, or in any other manner, any valid and enforceable claim of the '720 and '277 Patents either literally or under the doctrine of equivalents. Furthermore, Ravgen is precluded under the doctrines of disclaimer and prosecution history estoppel from asserting a scope for any claim of the '720 and '277 Patents that would encompass the Panorama, Vistara, Signatera, and Prospera tests because of admissions, amendments, and statements made to the USPTO during prosecution of the applications leading to the issuance of the '720 and '270 Patents or related family members. Ravgen is also precluded under the ensnarement doctrine from asserting a scope for any claim of the '720 and '277 Patents that would encompass the prior art.

105. Invalidity. One or more claims of the '720 and '277 Patents are invalid because they fail to satisfy the conditions of patentability specified in Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103, and/or 112.

106. Unenforceability of the '720 and '277 Patents. The '720 and '277 Patents are unenforceable due to inequitable conduct. In particular, during prosecution of the applications that matured into the '720 and '277 Patents, Ravgen violated its duty of candor to the United States Patent & Trademark Office ("USPTO") and intentionally made false statements in support of patentability. *See infra* at Counterclaim Five.

107. Statutory Damages Limitation. Ravgen's claim for damages is statutorily limited by 35 U.S.C. §§ 286, 287 and/or 288.

108. No Entitlement to Injunctive Relief. Ravgen's claim for injunction relief is barred at least because Ravgen has not suffered any irreparable injury and because Ravgen has an adequate remedy at law.

109. Natera's investigation of its defenses is continuing, and Natera expressly reserves the right to assert any additional defenses under the Federal Rules of Civil Procedure, the patent laws of the United States, and any other defense, at law or in equity, that may now exist or be available in the future based upon discovery and further investigation in this case.

COUNTERCLAIMS

110. Counterclaimants Natera, Inc. and NSTX, Inc. ("Natera"), on personal knowledge as to its own acts, and on information and belief as to all others based on its own and its attorneys' investigation, alleges its Counterclaims against Ravgen, Inc. ("Ravgen") as follows:

NATURE OF THE ACTION

111. These Counterclaims arise from Ravgen's baseless allegation of infringement of U.S. Patent Nos. 7,727,720 ("'720 Patent") and 7,332,277 ("'277 Patent").

PARTIES

112. Natera is a corporation organized under the laws of Delaware, having its principal place of business in San Carlos, CA.

113. According to Ravgen's Complaint, Ravgen is a corporation organized under the laws of Delaware, having its principal place of business in Columbia, MD.

JURISDICTION

114. This Court has jurisdiction over the subject matter of these Counterclaims under, without limitation, 28 U.S.C. §§ 1331, 1367, 1338(a), 2201, and 2202.

115. Ravgen has subjected itself to personal jurisdiction by suing Natera in this Court.

VENUE

116. Venue is proper in this District pursuant to 28 U.S.C. § 1391.

117. Ravgen has consented to venue in this Court by filing its claims for patent infringement in this Court, in response to which these counterclaims are asserted.

ACTUAL CONTROVERSY

118. According to Ravgen's Complaint, Ravgen claims to be the assignee and owner of all rights, title to, and interest in United States Patent Nos. 7,727,720 ("the '720 Patent") and 7,332,277 ("the '277 Patent"). D.I. 1 at ¶¶ 36, 38. Ravgen has alleged that Natera has infringed and is infringing the '720 and '277 Patents, which Natera denies.

119. An actual controversy within the meaning of 28 U.S.C. §§ 2201 and 2202 exists between Ravgen and Natera. Natera seeks a declaration that it has not infringed and does not infringe the '720 and '277 Patents and that the '720 and '277 Patents are invalid.

COUNTERCLAIM ONE
(DECLARATORY JUDGEMENT OF NON-INFRINGEMENT OF THE '720 PATENT)

120. Natera repeats and re-alleges the allegations of the preceding paragraphs of these Counterclaims as if fully set forth herein.

121. Although Ravgen alleges in its Complaint that (i) Natera has infringed or continues to infringe the claims of the '720 Patent literally or under the doctrine of equivalents, (ii) Natera actively, knowingly, and intentionally has induced, and continues to actively, knowingly, and intentionally induce infringement of the '720 Patent, and (iii) Natera has contributed to and continues to contribute to the infringement by third parties of the '720 Patent, Natera has not infringed and does not infringe any valid claims of the '720 Patent under any theory of infringement.

122. A judicial determination of the respective rights of the parties with respect to the infringement of the claims of the '720 Patent is now necessary and appropriate under 28 U.S.C. § 2201.

COUNTERCLAIM TWO
(DECLARATORY JUDGEMENT OF INVALIDITY OF THE '720 PATENT)

123. Natera repeats and re-alleges the allegations of the preceding paragraphs of these Counterclaims as if fully set forth herein.

124. The claims of the '720 Patent are invalid under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

125. The claims of the '720 Patent are invalid under 36 U.S.C. §§ 102 and/or 103 in light of prior art. For example, one or more claims of the '720 Patent are invalid due to the following prior art: (i) Kiessling et al, U.S. Patent No. 6,618,664, (ii) *Amicucci et al., Prenatal Diagnosis of Myotonic Dystrophy Using Fetal DNA obtained from Maternal Plasma*, Clinical Chemistry 46(2) (2000), and (iii) Saito et al., *Prenatal DNA Diagnosis of a Single-Gene Disorder from Maternal Plasma*, The Lancet 356, 1170 (2000).

126. The claims of the '720 Patent are invalid under 35 U.S.C. § 112 for failing to comply with one or more of the written description requirement, the enablement requirement, and the definiteness requirement.

127. A judicial determination of the respective rights of the parties with respect to the infringement of the claims of the '720 Patent is now necessary and appropriate under 28 U.S.C. § 2201.

COUNTERCLAIM THREE
(DECLARATORY JUDGEMENT OF NON-INFRINGEMENT OF THE '277 PATENT)

128. Natera repeats and re-alleges the allegations of the preceding paragraphs of these Counterclaims as if fully set forth herein.

129. Although Ravgen alleges in its Complaint that (i) Natera has infringed or continues to infringe the claims of the '277 Patent literally or under the doctrine of equivalents, (ii) Natera actively, knowingly, and intentionally has induced, and continues to actively, knowingly, and intentionally induce infringement of the '277 Patent, and (iii) Natera has contributed to and continues to contribute to the infringement by third parties of the '277 Patent, Natera has not infringed and does not infringe any valid claims of the '277 Patent under any theory of infringement.

130. A judicial determination of the respective rights of the parties with respect to the infringement of the claims of the '277 Patent is now necessary and appropriate under 28 U.S.C. § 2201.

COUNTERCLAIM FOUR
(DECLARATORY JUDGEMENT OF INVALIDITY OF THE '277 PATENT)

131. Natera repeats and re-alleges the allegations of the preceding paragraphs of these Counterclaims as if fully set forth herein.

132. The claims of the '277 Patent are invalid under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

133. The claims of the '277 Patent are invalid under 36 U.S.C. §§ 102 and/or 103 in light of prior art. For example, one or more claims of the '277 Patent are invalid due to the following prior art: (i) Umansky et al, U.S. Patent Publication No. 2002/0119478, (ii) Jones et al., U.S. Patent Publication No. 2003/0082576, and (iii) *Saiki et al., Diagnosis of Sickle Cell Anemia and Beta-thalassemia with Enzymatically Amplified DNA and Non-radioactive Allele-specific Oligonucleotide Probes*, New England Journal of Medicine 46(2), 301-302 (1988).

134. The claims of the '277 Patent are invalid under 35 U.S.C. § 112 for failing to comply with one or more of the written description requirement, the enablement requirement, and the definiteness requirement.

135. A judicial determination of the respective rights of the parties with respect to the infringement of the claims of the '277 Patent is now necessary and appropriate under 28 U.S.C. § 2201.

COUNTERCLAIM FIVE
(DECLARATORY JUDGMENT OF INEQUITABLE CONDUCT)

136. On information and belief, the Patents-in-Suit are unenforceable because they were procured from the U.S. Patent and Trademark Office (the "PTO") through inequitable conduct, comprising the failure of one or more persons associated with the filing of the Patents-in-Suit to satisfy their duty of candor and good faith under 37 C.F.R. § 1.56.

137. On information and belief, the named inventors, attorneys, or agents who prepared or prosecuted the applications leading to the issuance of the '277 and '720 patents, or other persons who were substantively involved in the preparation or prosecution of these applications (collectively, the "Applicant") were aware of information material to the patentability of the claims of the '277 and '720 patents, but withheld that information from the PTO with intent to deceive.

138. [redacted]

139. The '277 patent issued from U.S. Patent Application No. 10/661,165 (the "'165 application") (Exhibit A). The '165 application was filed on September 11, 2003, and the prosecution of that application continued through February 19, 2008. The Applicants owed a duty of candor to the PTO with respect to the '165 application throughout that entire period of time.

140. The ’720 patent issued from U.S. Patent Application No. 11/212,812 (the ’812 application) (Exhibit B). The ’812 application was filed on August 26, 2005, and the prosecution of that application continued through June 1, 2010. The Applicants owed a duty of candor to the PTO with respect to the ’812 application throughout that entire period of time.

A. The Applicant had information that contradicted its allegedly “unexpected results” presented in both the ’165 and ’812 applications and withheld that information from the PTO with the intent to deceive.

141. C.F.R. § 1.56 requires Applicants to disclose “all information known to that individual to be material to patentability as defined in this section.” Information is material when it “refutes, or is inconsistent with, a position the applicant takes in . . . asserting an argument of patentability.” C.F.R. § 1.56(b). Thus, the Applicant had an obligation to the PTO to disclose information inconsistent with any arguments of patentability made before the office.

142. On information and belief, the Applicant was aware of deficiencies with its experimental methodologies as described in his applications. These deficiencies falsely inflated the cell free fetal DNA amounts reported in the specifications.

143. On information and belief, despite knowing that the experiments falsely inflated the amount of cell-free fetal DNA it observed, the Applicant presented its incorrect results to the Examiner as evidence of “unexpected” results.

144. [redacted]

145. But for the Applicant’s deceit, the Examiner would not have allowed one or more claims. The Examiner explained on several occasions that certain claims in the ’277 and ’720 patents were obvious “absent unexpected results.” [redacted]

[redacted]

146. The Applicant's violation of its duty of candor and good faith constitutes inequitable conduct. The Applicant knowingly withheld and misrepresented information that was but-for material to the patentability of one or more claims in the '277 and '720 patents, and it withheld and misrepresented that information with the specific intent to deceive the PTO. The '277 and '720 patents are therefore unenforceable.

1. [redacted]

147. [redacted]

148. [redacted]

149. [redacted]

150. On March 3, 2004, the Journal of the American Medical Association published an article by Dr. Dhallan. In the article, Dr Dhallan reported that the addition of formaldehyde to maternal blood samples increased the percentage of cell-free fetal DNA isolated from those blood samples. Exhibit D at 1.

151. On March 1, 2005, the peer-reviewed journal Clinical Chemistry published an article by Dr. Hahn of the University Woman's Hospital in Switzerland. Exhibit E at 652–55 ("Chinnapapagari"). In the article, Dr. Hahn "sought to verify [Dr. Dhallan's] report and have investigated whether the addition of formaldehyde to maternal blood samples does indeed significantly alter the proportion of fetal DNA in maternal plasma samples." *Id*. at 652. Dr. Hahn tested four different methods:

A. Method exactly as described by Dhallan et al. (16) (formaldehyde treatment)
B. Method described by Dhallan et al. minus formaldehyde
C. Our routine centrifugation procedure plus the addition of formaldehyde
D. Our routine centrifugation procedure (without formaldehyde)

Id. at 653.

152. At the conclusion of his experiments, Dr. Hahn was "not able to discern any effect of formaldehyde on the proportion of fetal DNA (Table 1 and Fig. 1C). *Id*. at 654. Dr. Hahn concluded that "[o]ur data therefore do not support the report by Dhallan et al. *(16)*, which stated that formaldehyde treatment led to an increase in the proportion of cell-free fetal DNA in maternal plasma samples of 20–50% or more. *Id*. at 654.

153. In that same March 1, 2005 issue of Clinical Chemistry, Dr. Lo—the discoverer of cell free fetal DNA—described his attempt to "validate and investigate the underlying mechanisms" of Dr. Dhallan's claimed method. Exhibit F at 655 ("Chung"). Dr. Lo engaged in an analysis conducted in three stages: 1) "verify the effects of the previously published protocol," 2) "evaluate the effects of formaldehyde addition on total and fetal DNA concentrations . . . in

relation to the time of blood processing," and 3) "investigate[] whether the reported enrichment might be a consequence of the imprecision of the analytical method chosen by the authors." *Id*.

154. Dr. Lo's experiments explained that Dr. Dhallan's method provided only a:

> small (1–3.3% increase in median values; Table 1) but nonsignificant increase in the fractional fetal DNA concentrations at each of the time-points in both the second (P = 0.237, Friedman) and third trimesters (P = 0.339, Friedman) of pregnancy (Table 1). **These data contrast markedly with the extent of fetal DNA enrichment reported previously** [by Dhallan] (59% of samples with fetal DNA percentages >25% with a range extending to >50%).

Id. at 657 (emphasis added).

155. Dr. Lo also sought to "investigate the cause of the discrepancy" between his results and Dr. Dhallan's results. *Id*. Dr. Lo compared the "serial dilution method used in [Dhallan's] study" with "RQ-PCR." *Id*. In his analysis, Dr. Lo found that because of the "categorical nature" of serial dilution, "the data would be skewed and inaccurately represented." *Id*. Dr. Lo concluded that:

> **formaldehyde addition did not yield the previously reported dramatic increases in fraction concentrations of fetal DNA** *(7)*. The latter could have resulted from the imprecise estimation of the fetal DNA percentages in maternal plasma when the previously reported serial dilution method was used.

Id. at 658.

156. On February 10, 2007, the *Lancet* published a report authored by Dr. Dhallan. Exhibit G at 474. Dr. Dhallan reported using "formaldehyde-treated blood samples from 60 pregnant woman and the stated biological fathers." *Id*. at 474. Dr. Dhallan further wrote that he "previously reported that the careful sample processing and the addition of formaldehyde increased the proportion of free fetal DNA recovered from the maternal circulation to about 25%." *Id*.

157. On June 16, 2007, the *Lancet* published three letters from researchers responding to Dr. Dhallan's February 2007 publication. Exhibit H at 1997. One scientist, Dr. Hulten, explained that Dr. Dhallan's protocol "could not be reproduced by two interim studies", and "[i]t

is curious that there is no mentioning of this controversy in the *Lancet* paper." *Id*. Dr. Lo wrote that "[f]irst and foremost, the controversy surrounding fetal DNA enrichment by formaldehyde is not mentioned." *Id*. (citations omitted). And finally, Dr. Hahn explained that, because other laboratories could not replicate Dr. Dhallan's results, Dr. Dhallan's "report in its current form could be too preliminary." *Id*. at 1998. *Chung* and *Chinnapapgari* were both cited in all of the letters.

158. On June 16, 2007, the Lancet published a letter by Dr. Dhallan responding to the comments made by Drs. Hulten, Lo, and Hahn. *Id*.

159. [redacted]

160. On information and belief, the Applicant was also aware of both the *Chung* and *Chinnapapagari* publications.

161. On information and belief, the Applicant was aware that *Chung* explained why the Applicant's methodology resulted in incorrect, inflated, cell-free fetal DNA values.

162. On information and belief, the Applicant was also aware that other persons in the art regarded the *Chung* and *Chinnapapagari* publications as significant enough to write to the *Lancet* in comment.

163. On information and belief, the Applicant was aware of information contesting its unexpected results—and the significance of that information—while it had a duty of candor to the PTO.

2. [redacted]

164. The Applicant disclosed 453 documents in connection with the '165 application prosecution. *See* Exhibits I–V. The Applicant disclosed 428 documents in connection with the '812 application. *See* Exhibits W & X.

165. [redacted]

166. In fact, the Applicant argued to the PTO that:

> Applicant has discovered that the addition of a cell lysis inhibitor during the sample preparation process can **significantly and unexpectedly increase the proportion of fetal DNA** versus maternal DNA obtained from a sample such as a plasma sample obtained from the blood of a pregnant woman.

Exhibit Y, Response dated July 14, 2006 at 31–32; *see also* Exhibit Z, Response dated May 30, 2007 at 36 (internal citations omitted, emphasis added). [redacted]

167. On information and belief, the Applicant knew that the "unexpected results" it observed were caused by its highly-inaccurate measuring method.

168. On information and belief the Applicant, with the intent to mislead the PTO, refused to turn contradictory information over to the Examiner.

3. The Applicant was aware that evidence of unexpected results was highly material to the allowance of the '277 and '720 patents.

169. On March 17, 2006, Examiner Whisenant issued a non-final rejection of the claims of the '165 application as being obvious by *Lo* et al. (WO98/39474) in view of *Wallace* et al. (US 5,639,611) or *Jones* et al. (US2003/0082576). Exhibit AA, Office action dated March 17, 2006 at 8. Examiner Whisenant explained that "**absent an unexpected result** it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method

of Lo et al. wherein the sequence of a locus of interest (i.e. the allele status of the ß-globin gene) is determined." *Id*. (emphasis added).

170. On July 14, 2006, the Applicant explained that "[a]s indicated in the application, Applicant has discovered that the addition of a cell lysis inhibitor during the sample preparation process can **significantly and unexpectedly increase the proportion of fetal DNA** versus maternal DNA obtained from a sample such as a plasma sample obtained from the blood of a pregnant woman." Exhibit Y, Response dated July 14, 2006 at 31–32 (emphasis added).

171. On January 30, 2007, the Examiner of the '165 application issued a non-final rejection of the claims of the '165 application. Exhibit AB, office action dated January 30, 2007. The Examiner rejected claims directed to the agent that inhibits lysis of cells "as being unpatentable over Umansky et al [U.S. 2002/0119478(2002)] in view of Kiessling [U.S. 5,618,664(1998)]." *Id*. at 18. In particular, the Examiner found:

> "Umansky et al. teach a method comprising all of the limitations of Claim 58 except these authors do not each adding an agent that inhibits cell lysis to their maternal urine samples. However, Kiessling does teach adding an agent to a biological sample which simultaneously disinfects and inhibits the lysis of cells therein. Therefore **absent an unexpected result**, it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the method of Umansky et al. wherein the maternal urine sample is treated according to the method of Kiessling.

Id. at 19 (emphasis added).

172. In its response, the Applicant explained:

> "[a]nalysis of free fetal DNA in the maternal circulation provides an alternative to existing prenatal tests. However, the seemingly low percentage of free fetal DNA in the maternal circulation (initial studies reported a mean of only 3.4% free fetal DNA in the mid to late first trimester) has limited the clinical utility of free fetal DNA. The methods encompassed within claims 58–68, 87–102, 190–196 and 201 [alleviate] this problem, and thus provide a solution to a long-felt need in the medical community.
>
> Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to determining the sequence of a locus of interest on free fetal DNA can

> **significantly and unexpectedly increase the proportion of fetal DNA** versus maternal DNA obtained from a sample such as a plasma sample obtained from the blood of a pregnant woman.

Exhibit Z, Response dated May 30, 2007 at 35–36 (internal citations omitted, emphasis added).

173. On December 17, 2007 the Applicant filed a response to office action in for the '812 application. There, the Applicant explained:

> Methods for detecting free nucleic acid as claimed in claims 1–9, 26–28 may be useful in identifying early stage diseases, including, but not limited to, detecting tumors. However, typically, samples contain only small amounts of free nucleic acid, which has limited the clinical utility of free nucleic acid. The methods encompassed within claims 1–9 and 26–28 [alleviate] this problem, and thus provide a solution to a long-felt need in the medical community.
>
> Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to detecting the presence of free nucleic acid can **significantly and unexpectedly increase the proportion of free nucleic acid** obtained from the sample.

Exhibit AC, Response to office action dated December 17, 2007 at 13–14 (internal citations omitted, emphasis added).

174. On March 14, 2008, Examiner Whisenant issued a final rejection of the claims of the '812 application. Exhibit AD, Office action dated March 14, 2008 at 2 (emphasis added). In the rejection, the Examiner explained that "[c]laim(s) 1–23 and 26–32 is/are deemed to be allowable in light of the applicant's amendment filed 17 DEC 07 and the persuasive argument(s) therein. **The most persuasive argument(s) related to** the applicant assertion that there was a long felt need and **the evidence of an unexpected result on pages 13 and 14** of the applicant's response." *Id*.

175. On information and belief, Applicant knew that the increased percentage of cell-free fetal DNA reported in the specifications of the '165 and '812 patents were material to the patentability of certain claims in both the '165 and '812 patents. [redacted]

[redacted]

176. Thus, the Applicant violated its duty of candor and good faith to the PTO resulting in inequitable conduct. Both the '277 and '720 patents are therefore unenforceable.

B. [redacted]

177. C.F.R. § 1.56 requires Applicants to disclose "all information known to that individual to be material to patentability as defined in this section." Information is material when it "refutes, or is inconsistent with, a position the applicant takes in . . . opposing an argument of unpatentability relied on by the office." C.F.R. § 1.56(b). Thus, the Applicant had an obligation to the PTO to disclose information inconsistent with any positions the Applicant took before the PTO rebutting the PTO's arguments.

178. During prosecution of the '277 patent, the Examiner issued a rejection of one or more of the pending claims as anticipated over a prior art reference that taught the use of the compound EDTA. Exhibit AA, Office action dated March 17, 2006 at 5. The Examiner characterized EDTA as an agent that inhibits cell lysis. *Id.*

179. [redacted]

180. [redacted]

181. But for the Applicant's deceit, the Examiner would not have allowed one or more claims of the '277 patent.

182. The Applicant's violation of his duty of candor and good faith constitutes inequitable conduct. The applicant knowingly misrepresented information that was but-for material to the patentability of one or more claims in the '277 patents, and he misrepresented that information with the specific intent to deceive the PTO. The '277 patent is therefore unenforceable.

183. The claims and prosecution of the '720 patent shares an immediate and necessary relationship with the inequitable conduct that occurred in connection with the '165 application. The '720 patent was a continuation-in-part of the '165 application and was also examined by Examiner Whisenant. The Applicant's egregious affirmative misconduct in mischaracterizing the properties of EDTA infected Examiner Whisenant's examination of the application that issued as the '720 patent. The '720 patent is therefore unenforceable under the doctrine of infectious unenforceability.

1. [redacted]

184. [redacted]

185. [redacted]

[redacted]

2. [redacted]

186. On March 17, 2006, Examiner Whisenant rejected Claim 87 of the '165 application "as being anticipated by Lo et al. [WO98/39474 (SEP 1998)]." Exhibit AA, Office action dated March 17, 2006 at 5. The Examiner explained that:

> "Lo et al. teach[es] a method for preparing a sample for analysis comprising all of the limitations recited in Claims 87–95, 100, and 102. Note pp. 6–8 wherein Lo et al. teach collecting maternal blood into a tube comprising EDTA (i.e. agent that inhibits cell lysis).

Id.

187. [redacted]

188. [redacted]

[redacted]

189. On information and belief, the Applicant made a deliberate decision to provide the PTO with false information to advance prosecution of the '165 application.

3. The Applicant's misrepresentations were but-for material to the patentability of at least some claims of the '277 patent.

190. Examiner Whisenant's March 17, 2006 rejection of Claim 87 of the '165 application was refuted by Ravgen exclusively on the basis of its argument that EDTA was not an "agent that inhibits cell lysis." Exhibit Y, Response to office action dated July 14, 2006 at 33.

191. But for that argument, claim 87 of the '165 application would have been rejected as anticipated. The Applicant did not contest that the *Lo* reference lacked any other elements of claim 87. *See*, *e.g.*, *id*. [redacted] The '277 patent is therefore unenforceable.

4. The Applicant's misconduct infected the prosecution of the '720 patent.

192. The '720 patent issued as a continuation-in-part of the'165 application ('277 patent). Examiner Whisenant examined both the '165 application and the application that issued as the '720 patent.

193. [redacted]

194. [redacted] The

affirmative egregious misconduct of the Applicant during the prosecution of the '165 application was therefore material to at least claim 1 of the '720 patent.

C. The Applicant committed a fraud on the PTO by misrepresenting the results of both Examples 4 and 15 of the Asserted Patents.

195. C.F.R. § 1.56 provides "no patent will be granted on an application in connection with which fraud on the Office as practiced or attempted." Thus, the Applicant had an obligation to the PTO to avoid making any intentionally false statements during prosecution.

196. During prosecution of the '165 application, the Examiner issued a rejection of one or more pending claims over a prior art reference that taught the use of the compound EDTA. Specifically, the Examiner stated that the compound EDTA was an "agent that inhibits cell lysis."

197. In response to the rejection, the Applicant intentionally misrepresented the results of the experiments described in Examples 4 and 15, and stated that the two examples proved that EDTA did not inhibit cell lysis.

198. The Applicant's violation of its duty of candor and good faith constitutes inequitable conduct. The Applicant knowingly misrepresented information that was but-for material to the patentability of one or more claims in the '277 patent, and it misrepresented that information with the specific intent to deceive the PTO. The '277 patent is therefore unenforceable.

199. The claims and prosecution of the '720 patents shares an immediate and necessary relationship with the inequitable conduct that occurred in connection with the '165 application. The '720 patent was a continuation-in-part of the '165 application and was also examined by Examiner Whisenant. The Applicant's egregious affirmative misconduct in mischaracterizing the properties of EDTA infected Examiner Whisenant's examination of the application that issued as

the '720 patent. The '720 patent is therefore unenforceable under the doctrine of infectious unenforceability.

1. Examples 4 and 15 of the Asserted Patents cannot show that EDTA is not a cell lysis inhibitor.

200. As explained by the experts retained by both Natera and Ravgen, neither Example 4 nor Example 15 can show that EDTA is not a cell lysis inhibitor. For example, Dr. Grody stated that:

> "[t]he experiments described in Examples 4 and 15 did not test the effectiveness of EDTA at preventing cell lysis. In fact, if that were the intent, the experiments would have compared the amount of cell lysis in tubes with no EDTA to the amount of cell lysis in tubes with EDTA alone. . . . No such experiments were described in the specifications."

D.I. 46-1 at ¶ 55.

201. Similarly, Dr. Quackenbush explained that, because EDTA was "in the control sample, this experiment cannot determine whether or not EDTA is a cell lysis inhibitor." D.I. 49-1 at ¶ 39.

202. On information and belief, the Applicant would understand that an experiment that includes EDTA in its control sample would not be able to determine whether or not EDTA was an agent that inhibits cell lysis.

2. The Applicant falsely told the PTO that Examples 4 and 15 of the Asserted Patents demonstrate that EDTA is not an agent that inhibits cell lysis.

203. On March 17, 2006, Examiner Whisenant rejected Claim 87 of the '165 application "as being anticipated by Lo et al. [WO98/39474 (SEP 1998)]." Exhibit AA, Office action dated March 17, 2006 at 5. The Examiner explained that:

> "Lo et al. teach[es] a method for preparing a sample for analysis comprising all of the limitations recited in Claims 87–95, 100, and 102. Note pp. 6–8 wherein Lo et al. teach collecting maternal blood into a tube comprising EDTA (i.e. agent that inhibits cell lysis).

Id. at 5.

204. On July 14, 2006, the Applicant responded to the Examiner's rejection by stating that the results of Example 4 demonstrated that EDTA was not a cell lysis inhibitor, and thus distinguished the claimed invention from the prior art:

> As shown in Example 4, discussed above, the addition of formalin, even in the presence of EDTA, to samples has a dramatic effect on the percentage of free fetal DNA isolated from the samples. **The fact that the addition of formalin can have such a dramatic effect on the percentage of free fetal DNA serves to demonstrate that formalin and EDTA have very different properties** and cannot be equated to each other.

Exhibit Y, Response to office action dated July 14, 2006 at 33 (emphasis added).

205. The statements the Applicant made to the PTO are directly contradicted by basic scientific understanding, as explained by Drs. Grody and Quackenbush. *See supra* at ¶¶ 200 & 201.

206. On information and belief, the Applicant was aware of the falsity of its statements, but made those statements in an effort to defraud the PTO.

3. The Applicant's false statements characterizing Examples 4 and 15 were material.

207. Examiner Whisenant's March 17, 2006 rejection of Claim 87 of the '165 application was refuted by Ravgen exclusively on the basis of its argument that EDTA was not an "agent that inhibits cell lysis." Exhibit Y, Response to office action dated July 14, 2006 at 33. As part of its support for that position, the Applicant stated that Example 4 confirmed that "formalin and EDTA have very different properties and cannot be equated to each other." *Id*.

208. But for the Applicant arguing that EDTA is not a cell lysis inhibitor, claim 87 of the '165 application would have been rejected. The Applicant did not contest that the *Lo* reference lacked any other elements of claim 87. *See*, *e.g.*, *id*. Thus, the Applicant's misrepresentation that Example 4 supported its assertion that EDTA was not an "agent that inhibits cell lysis" was

material, violating the Applicant's duty of candor and good faith to the PTO and resulting in inequitable conduct. The '277 patent is therefore unenforceable.

4. The Applicant's misconduct infected the prosecution of the '720 patent.

209. The '720 patent issued as a continuation-in-part of the'165 application ('277 patent). Examiner Whisenant examined both the '165 application and the application that issued as the '720 patent.

210. On information and belief, Examiner Whisenant considered the information submitted during the prosecution of the '165 application, including the arguments that EDTA was not a cell lysis inhibitor.

211. On information and belief, Examiner Whisenant did not consider Lo, in combination with other references, to reject at least claim 1 of the '720 patent in part because of the misstatements made by the Applicant during the prosecution of the '165 application. The affirmative egregious misconduct of the Applicant during the prosecution of the '165 application was therefore material to at least claim 1 of the '720 patent.

JURY DEMAND

212. Pursuant to Federal Rule of Civil Procedure 38, Natera demands a trial by jury on all issues so triable in this action.

REQUEST FOR RELIEF

WHEREFORE, Natera respectfully requests the following relief:

A. That Ravgen take nothing by its Complaint;

B. That judgment be entered against Ravgen and in favor of Natera;

C. That Ravgen's Complaint be dismissed with prejudice;

D. That the Court declare that Natera does not infringe and has not infringed, directly, indirectly, or under the doctrine of equivalents, any claim of the '720 and/or '277 Patents;

E. That the Court declare each claim of the '720 and/or '277 Patents is invalid and/or unenforceable;

F. That this case be declared exceptional and Natera be awarded its costs, expenses, and reasonable attorneys' fees in this action under 35 U.S.C. § 285; and

G. That the Court grant Natera such further relief the Court may deem just and proper.

Respectfully submitted,

Dated: May 04, 2021

/s/ Stephen M. Hash

Stephen M. Hash (#1014)
Texas Bar No. 24012800
Samoneh Kadivar
Texas Bar No. 24097911
BAKER BOTTS L.L.P.
98 San Jacinto Blvd., Suite 1500
Austin, Texas 78701
Phone: (512) 322-5471
Fax: (512) 322-3622
stephen.hash@bakerbotts.com
samoneh.kadivar@bakerbotts.com

Elizabeth Durham Flannery
Texas Bar No. 24045815
BAKER BOTTS L.L.P.
One Shell Plaza
910 Louisiana Street
Houston, TX 77002-4995
Telephone: (713) 229-1234
liz.flannery@bakerbotts.com

ATTORNEYS FOR
NATERA, INC. AND NSTX, INC.

CERTIFICATE OF SERVICE

I hereby certify that the following counsel of record who have consented to electronic service are being served on this 4th day of May 2021, with a copy of this by electronic mail.

Deron R. Dacus
State Bar No. 00790553
THE DACUS FIRM, P.C.
821 ESE Loop 323, Suite 430
Tyler, TX 75701
Phone: (903) 705-1117
Fax: (903) 581-2543
ddacus@dacusfirm.com

OF COUNSEL:

John M. Desmarais (*pro hac vice*)
Kerri-Ann Limbeek (*pro hac vice*)
Kyle Petrie *(pro hac vice)*
Jamie L. Kringstein *(pro hac vice)*
Karl Mullen (*pro hac vice*)
Raymond N. Habbaz (*pro hac vice*)
Julianne M. Thomsen *(pro hac vice)*
Mike Ling (*pro hac vice*)
DESMARAIS LLP
230 Park Avenue
New York, NY 10169
Phone: (212) 351-3400
Fax: (212) 351-3401
jdesmarais@desmaraisllp.com
klimbeek@desmaraisllp.com
kpetrie@desmaraisllp.com
jkringstein@desmaraisllp.com
kmullen@desmaraisllp.com
rhabbaz@desmaraisllp.com
jthomsen@desmaraisllp.com
mling@desmaraisllp.com

/s/ Stephen M. Hash
Stephen M. Hash